canceled. Claims 1, 5, 13, 21-23, 40, 49-54 and 67-72 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Specification

The Examiner suggests that the reference to the address of the ATCC is incomplete at several places in the specification as filed. Applicants have amended the specification as requested at pages 48, 66, 69 and 73.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 49-72 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner suggests that the specification as filed while being enabling for a method of modulating expression of human and murine IL-5 and IL-5 receptor alpha genes *in vitro* does not enable *in vivo* uses of the claimed antisense compounds, nor does it enable a diagnostic kit for detecting expression levels of IL-5 receptor alpha. The Examiner cites several articles on the technology of

antisense to support the position regarding extrapolation to *in vivo* and pharmaceutical uses. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that the cited references support the position that application of antisense *in vivo* is unpredictable.

The Examiner has pointed to several articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in whole animals and humans.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Although this discusses some of the issues to be addressed in development of antisense as a pharmaceutical tool, no where does it teach that extrapolation from *in vitro* data to *in vivo* effects is unpredictable inherently as asserted by the Examiner.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The statements alluded to by the Examiner concerning extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are only one small part of this review paper. When read in its entirety the author is merely stating a well known fact in the development of any drug, not merely antisense. Pharmacokinetics is not the study of the pharmacological activity of an agent, such as is studied commonly in cells, but rather the study of the biological distribution of a drug in an animal or human. Therefore, the statements by the author do not demonstrate the unpredictability of antisense oligos *in vivo* but rather merely state the obvious, that one would not use studies on cellular uptake to predict pharmacokinetics in animals or humans because it is not a logical use of such data for any drug. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of drug development that data from whole cell studies, such as are provided in Example 15 of the instant specification, are directly applicable to predicting *in vivo* activity. The teachings of the paper by Crooke, as well as

the other cited paper (Branch), provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies or *in vivo* pharmacological studies in animals would not be predictive of activity *in vivo* in humans.

Additionally, the Examiner has failed to provide reasons for the rejection of claims 70-72 based on the cited references. Neither of the cited references teaches or suggests that activity to inhibit expression of IL-5 receptor alpha in cells would not be predictive of the successful development of a diagnostic kit. Since a kit is based on determining activity in either fluids or cells isolated from a patient, an *in vitro* type assay, it would be clear to one of ordinary skill in the art that data from *in vitro* experiments would be not only applicable but enabling. Further, at pages 23-24 of the specification as filed, such kit development is discussed.

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claims 49 and 51-54 to recite that the methods are performed *in vitro* and have canceled claims 55-66, with Applicants reserving the right to file a continuing application directed to this subject matter. Additionally, claims 67-69 have been amended to remove the term "pharmaceutical" and claims 70-72 have been amended to add the limitation of an "*in vitro*" diagnostic kit.

Applicants have not amended claim 50 to recite that the method is performed *in vitro*, however, because Applicants respectfully

point out that in the specification as filed, at pages 60-64, results of several *in vivo* studies are presented. Experiments were performed and presented in the specification as filed demonstrating that the antisense compounds of the instant invention were effective when given to animals *in vivo*. In one set of experiments, eosinophilia was prevented in mice dosed *in vivo* with antisense oligonucleotides. In another set of experiments, IL-5 levels were shown to be decreased in mice *in vivo* after pre-treatment with antisense compounds of the instant invention. In a third set of experiments, an art-accepted mouse model for human allergic asthma, the antisense compounds of the instant invention were shown to have therapeutic activity. Therefore, the specification as filed demonstrates that the compounds of the instant invention are pharmacologically active *in vivo* to reduce IL-5 levels and thus treat allergic asthma in an art-accepted animal model for human asthma.

Based on the arguments presented above and the amendments to the claims, withdrawal of the rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1-3, 7, 8, 49 and 50 have been rejected under 35 U.S.C. 102(b) as being anticipated by Weltman et al. (US Patent

6,048,726). The Examiner suggests that this patent discloses a 16 mer antisense oligonucleotide that modulates expression of mammalian IL-5 as well as inhibition of IL-5 signal transduction *in vitro* using said antisense compound. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to recite that the antisense compounds of the instant invention are either targeted to murine IL-5 nucleic acid molecules or are targeted to human IL-5 nucleic acid molecules within regions other than the full coding region of human IL-5. Support for these amendments to the claims can be found throughout the specification as filed but in particular at pages 46-113.

Weltman et al. (US Patent 6,048,726) disclose a 16 mer antisense oligonucleotide that has the ability to inhibit expression of IL-5 *in vitro*. The antisense compound was designed to be antisense to an area within the coding region of human IL-5. No other targets for antisense within the sequence of human IL-5 are taught by this reference. In addition, only one particular sequence for a coding region targeted antisense compound is taught.

MPEP 2131 states that in order to anticipate an invention the reference cited must teach each and every limitation of the cited claim. The patent of Weltman et al. fails to teach the limitations

of the amended claims and thus cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

Claims 5 and 51 have been rejected under 35 U.S.C. 102(b) as being anticipated by Nyce et al. (WO 96/40162). The Examiner suggests that this patent application discloses oligonucleotides of 8 to 30 mer targeted to human IL-5 receptor a as well as a method of inhibition of IL-5 receptor a through use of antisense targeted to this gene. Applicants respectfully traverse this rejection.

WO 96/40162 discloses the use of antisense oligonucleotides that are essentially adenosine-free to treat airway disease wherein the antisense are targeted to IL-5 receptor a and IL-5. Nowhere does this patent application teach or suggest antisense targeted to murine IL-5 receptor a or antisense targeted to specific regions of human IL-5 receptor a as now claimed. Further, none of the specific sequences of the instant invention are taught or suggested by this patent application. MPEP 2131 specifies that in order to anticipate an invention the reference cited must teach each and every limitation of the cited claim. The patent application of Nyce et al. fails to teach the limitations of the amended claims and thus cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

Claims 13 and 40 have been rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. (US Patent 6,210,892). The Examiner suggests that this patent discloses a 15 nucleobase portion of SEQ ID NO: 209. Applicants respectfully traverse this rejection.

Applicants have amended claim 13 and 40 to recite that the instant invention consists of SEQ ID NO: 209. Bennett et al. disclose a sequence that contains SEQ ID NO: 209 of the instant invention but does not consist of SEQ ID NO: 209. MPEP 2131 specifies that in order to anticipate an invention the reference cited must teach each and every limitation of the cited claim. The patent of Bennett et al. fails to teach the limitations of the amended claims and thus cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

Claim 4 has been rejected under 35 U.S.C. 102(b) as being anticipated by Dolgonov et al. (US Patent 5,821,091). The Examiner suggests that this patent discloses a 24 mer-sequence (SEQ ID NO: 14) having 100% homology with bases 1-20 of SEQ ID NO: 52 of the instant application. Applicants respectfully disagree with the Examiner's conclusions.

Careful review of the sequence in the Dolgonov patent and SEQ ID NO: 52 of the instant invention failed to reveal the claimed

100% homology referenced by the Examiner. MPEP 2131 specifies that in order to anticipate an invention the reference cited must teach each and every limitation of the cited claim. The patent of Dolgonov et al. fails to teach the claimed limitations and thus cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1-4, 7-23, 49 and 50 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Weltman et al., and further in view of Dolgonov et al., Sahasrabudhe et al. (1996), Baracchini et al. (US Patent 5,801,154), and Fritz et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to combine the teachings of Weltman et al., Dolgonov et al., Baracchini et al., and Fritz et al. to make the instant invention because Weltman teaches antisense to IL-5 and use of antisense to inhibit gene expression, Dolgonov teach an antisense compound with 100% homology to a sequence claimed, Baracchini et al. disclose modification of antisense as claimed, and Fritz et al. teach use of drug delivery systems as claimed for oligonucleotides. The Examiner suggests that motivation is provided by the teachings of Weltman and Dolgonov, while Baracchini, Fritz, and Sahasrabudhe

provide motivation for modification of oligonucleotides as claimed. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to recite specific regions within the nucleobase sequence of IL-5 nucleic acid molecules of specific SEQ ID NO's that are to be targeted by antisense compounds. These regions are taught in the specification as filed (as discussed in detail *supra*).

Weltman et al. (US Patent 6,048,726) discloses a single 16 mer antisense oligonucleotide that has the ability to inhibit expression of IL-5 *in vitro*. The antisense compound was designed to be antisense to an area within the coding region of human IL-5. No other targets for antisense within the sequence of human IL-5 are taught by this reference. In addition, only one particular sequence for a coding region targeted antisense compound is taught. Nowhere does this patent teach regions of IL-5 other than the coding region of human IL-5 that might be targeted specifically with antisense. Further, this patent fails to teach any of the specific sequences of the instant invention.

The secondary references cited fail to overcome the deficiencies in teaching of this primary reference.

As discussed *supra*, Dolgonov et al. fail to teach a specific sequence of the instant invention as claimed by the Examiner.

Therefore, this patent fails to teach or suggest the object of the instant invention as claimed and adds no teaching to support a case of *prima facie* obviousness.

Sahasrabudhe et al. (1996) discloses the effects of stereoisomerism at the point of attachment of a peptide to an oligonucleotide, as a conjugate. Nowhere does this patent teach or suggest antisense compounds targeted to regions of IL-5 nucleic acid molecules as claimed.

The '154 patent teaches modification to antisense oligonucleotides in general as a way to enhance activity. However, this general discussion of modified oligonucleotides does not teach or suggest use of antisense compounds of any type to target specific regions of an IL-5 nucleic acid molecule and the successful inhibition of expression using antisense.

Fritz et al. (1997) disclose and characterize model drug carrier systems for antisense oligonucleotides. However, nowhere does this paper teach or suggest antisense compounds targeted to regions of IL-5 nucleic acid molecules as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the

art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The claims as amended, which recite specific regions, other than the human coding region, within specific nucleic acids that encode IL-5, are not taught or suggested by any of the references individually or when combined. Therefore, present invention is not taught or suggested by the combination of prior art references, nor is any expectation of successful use of such region targeted antisense compounds provided by the combination of prior art. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

Claims 1, 2, 5-23, 49 and 51 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al., Bennett et al., Sahasrabudhe et al. (1996), Baracchini et al., and Fritz et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill in the art to make antisense to inhibit the expression of IL-5 receptor a since Nyce et al. teach the inhibition of this gene using antisense, because Bennett et al. teach an antisense compound that comprises SEQ ID NO: 209 of the instant invention, while Sahasrabudhe et al. (1996), Baracchini et

al., and Fritz et al. (1997) discloses ways to modify antisense as claimed. The Examiner suggests one of skill would be motivated to make such antisense compounds because Nyce et al. and Bennett et al. teach such antisense to IL-5 receptor a, while Sahasrabudhe et al. (1996), Baracchini et al., and Fritz et al. (1997) teach the use of modified oligonucleotides. Applicants respectfully traverse this rejection.

Nyce et al. (WO 96/40162) disclose the use of antisense oligonucleotides that are essentially adenosine-free to treat airway disease wherein the antisense are targeted to IL-5 receptor a and IL-5. Nowhere does this patent application teach or suggest antisense targeted to murine IL-5 receptor a or antisense targeted to specific regions of human IL-5 receptor a as now claimed. Further, none of the specific sequences of the instant invention are taught or suggested by this patent application.

Bennett et al. (US Patent 6,210,892) disclose a 15 nucleobase portion of SEQ ID NO: 209 that is contained within a larger antisense compound. Nowhere does this patent teach or suggest antisense to IL-5 receptor a as claimed which is targeted to specific regions of specific nucleic acid molecules that are identified by SEQ ID NO.

Sahasrabudhe et al. (1996) disclose the effects of stereoisomerism at the point of attachment of a peptide to an oligonucleotide, as a conjugate. Nowhere does this patent teach or suggest antisense compounds targeted to regions of IL-5 receptor a nucleic acid molecules as claimed.

The '154 patent teaches modification of antisense oligonucleotides in general as a way to enhance activity. However, this general discussion of modified oligonucleotides does not teach or suggest use of antisense compounds of any type to target specific regions of an IL-5 receptor a nucleic acid molecule and the successful inhibition of expression using antisense.

Fritz et al. (1997) disclose and characterize model drug carrier systems for antisense oligonucleotides. However, nowhere does this paper teach or suggest antisense compounds targeted to regions of IL-5 receptor a nucleic acid molecules as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

The limitations of the claims as now amended, which recite specific regions within specific nucleic acids that encode IL-5 receptor a, are not taught or suggested by any of the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful use of such region targeted antisense compounds provided by the combination of prior art. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The

Attorney Docket No.: ISPH-0537
Inventors: Dean et al.
Serial No.: 09/800,629
Filing Date: March 7, 2001
Page 24

attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **November 14, 2002**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

Attorney Docket No.: ISPH-0537
Inventors: Dean et al.
Serial No.: 09/800,629
Filing Date: March 7, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 3, 24-27 and 55-66 have been canceled.

The claims have been amended as follows:

1. (amended) An antisense compound 8 to 30 nucleobases in length which is targeted to a 5'-untranslated region, a coding region, a stop codon region, or a 3'-untranslated region of murine interleukin-5 of SEQ ID NO: 1 or a 5'-untranslated region, a stop codon region, or a 3'-untranslated region of a nucleic acid molecule encoding human interleukin-5 of SEQ ID NO: 78, wherein said antisense compound modulates murine or human interleukin-5 ~~signal transduction~~.

5. (amended) ~~The~~ An antisense compound ~~of claim 1~~ 8 to 30 nucleobases in length which is targeted to a 5'-untranslated region, a start codon region, a coding region, a stop codon region, or a 3'-untranslated region of a nucleic acid molecule encoding a ~~mammalian~~ murine interleukin-5 receptor a of SEQ ID NO: 132, a coding region or a 3'-untranslated region of a nucleic acid molecule encoding murine interleukin-5 receptor a of SEQ ID NO: 133, or a 5'-untranslated region, a coding region, a stop codon

region, or a 3'-untranslated region of a nucleic acid molecule encoding human interleukin-5 receptor a of SEQ ID NO: 176, wherein said antisense compound modulates the expression of ~~mammalian~~ murine or human interleukin-5 receptor a.

13. (amended) The antisense compound of claim 12 ~~comprising at least an 8-nucleobase portion~~ consisting of SEQ ID NO: 209.

21. (amended) A ~~pharmaceutical~~ composition comprising the antisense compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

22. (amended) The ~~pharmaceutical~~ composition of claim 21 further comprising a colloidal dispersion system.

23. (amended) The ~~pharmaceutical~~ composition of claim 21 wherein the antisense compound is an antisense oligonucleotide.

40. (amended) The antisense compound of claim 36 ~~comprising at least an 8-nucleobase portion~~ consisting of SEQ ID NO: 209.

49. (amended) A method of modulating interleukin-5 signal transduction in cells or tissues comprising contacting ~~said~~ cells or tissues *in vitro* with the antisense compound of claim 1 so that interleukin-5 signal transduction is modulated.

50. (amended) A method of modulating the expression of ~~mammalian~~ human or murine interleukin-5 in ~~mammalian~~ human or murine cells or tissues comprising contacting ~~said~~ human or murine

cells or tissues with the antisense compound of claim 3 so that expression of ~~mammalian~~ human or murine interleukin-5 is inhibited.

51. (amended) A method of modulating the expression of ~~mammalian~~ human or murine interleukin-5 receptor a in ~~mammalian~~ human or murine cells or tissues comprising contacting ~~said~~ human or murine cells or tissues *in vitro* with the antisense compound of claim 33 so that expression of ~~mammalian~~ human or murine interleukin-5 receptor a is inhibited.

52. (amended) A method of altering the ratio of the isoforms of ~~mammalian~~ human or murine interleukin-5 receptor a in ~~mammalian~~ human or murine cells or tissues comprising contacting ~~said~~ human or murine cells or tissues *in vitro* with the antisense compound of claim 33 so that the ratio of the ~~mammalian~~ human or murine interleukin-5 receptor a isoforms is altered.

53. (amended) A method of modulating the expression of ~~mammalian~~ human or murine interleukin-5 receptor a in ~~mammalia~~ human or murine cells or tissues comprising contacting ~~said~~ human or murine cells or tissues *in vitro* with the antisense compound of claim 5 so that expression of ~~mammalian~~ human or murine interleukin-5 receptor a is inhibited.

54. (amended) A method of altering the ratio of the isoforms of ~~mammalian~~ human or murine interleukin-5 receptor a in ~~mammalian~~

human or murine cells or tissues comprising contacting ~~said~~ human or murine cells or tissues *in vitro* with the antisense compound of claim 31 so that the ratio of the ~~mammalian~~ human or murine interleukin-5 receptor a isoforms is altered.

67. (amended) The ~~pharmaceutical~~ composition of claim 21 further comprising a chemotherapeutic agent for the treatment of asthma.

68. (amended) A ~~pharmaceutical~~ composition comprising the antisense compound of claim 28 and a pharmaceutically acceptable carrier or diluent.

69. (amended) A ~~pharmaceutical~~ composition comprising the antisense compound of claim 36 and a pharmaceutically acceptable carrier or diluent.

70. (amended) An *in vitro* diagnostic kit for detecting the expression level of ~~the~~ a membrane versus a soluble form of IL-5 Rreceptor a.

71. (amended) The *in vitro* diagnostic kit of claim 70 comprising the antisense compound of claim 33.

72. (amended) The *in vitro* diagnostic kit of claim 71 wherein the antisense compound is a peptide nucleic acid.